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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,571	02/02/2007	Samir Mitragotri	1279-407	6636

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EXAMINER	
LUNDGREN, JEFFREY S	
ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,571	MITRAGOTRI ET AL.	
	Examiner	Art Unit	
	JEFFREY S. LUNDGREN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *1-35,39-43 and 47-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-38 and 44-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election of Invention

In response to the Restriction Requirement, Applicants have elected the invention of Group III, claims 36-38 and 44-46, without traverse.

Claims 1-52 are pending in the instant application; claims 1-35, 39-43 and 47-52 are withdrawn from consideration; claims 36-38 and 44-46 are the subject of the Office Action below.

Objection to the Abstract Under 37 C.F.R. § 1.72

The abstract of the disclosure is objected to because it does not allow the public generally to determine quickly from a cursory inspection the nature and gist of the invention. Applicants should amend the abstract so that it corresponds to at least one independent claim. For example, Applicants should describe a formulation similar to either claim 36 or claim 44. *See* 37 C.F.R. § 1.72. Should Applicants amend the claims in their next reply, the amended abstract should take into account any further limitations added to the broadest independent claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 44-46 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44, and dependent claims 45 and 46, are indefinite for recitation of the phrase "acceptable irritation potential" because one of ordinary skill in the art could not reasonably determine the metes and bounds of this limitation. This phrase is a relative term of art, and does not clearly define a metric or quantitative measure that one of ordinary skill in the art could rely upon. Similarly, claim 45 is indefinite for reciting the phrase "irritation antergy factor" because one of ordinary skill in the art could not determine the metes and bounds.

Claim 44 is indefinite for reciting the phrase "skin conductivity enhancement ratio" because one of ordinary skill in the art could not reasonably determine the metes and bounds of this limitation. For example, it appears that the conductivity of the skin changes over time, and therefore the measurement at one time would not be the same as at another time (see paragraph 0058 in Applicants' specification).

Claim 46 is indefinite for reciting the phrases "azone and *related compounds*" and "solvents and *related compounds*" because one of ordinary skill in the art could not reasonably determine the metes and bounds. It is not clear from the claim, Applicants' own specification or the related art what "relatedness" is attributed to other compounds that Applicants are claiming.

Claim Rejections - 35 USC § 112 – Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-38 and 44-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to fully comply with the written description requirement. Although there may be certain examples of formulations falling within the scope of the claims, and Applicants may demonstrate certain formulation within the scope of the claims, the claims are generally so broad to be beyond the supported disclosure. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants' claims, such as claim 36, are directed towards all compositions that are formulations comprising a first and second chemical penetration enhancer having a 24-hour synergy value of 2 or more. However, Applicants specification only provides a limited number of working examples falling within the scope of the claims, such as certain combinations of sodium laurel ether sulfate and 1-phenyl piperazine, and combinations of N-lauryl sarcosine and Span 20/sorbitan monolaurate.

However, the art generally supports the notion that Applicants limited number of examples are not representative of all formulations. For example, see the publication by Karande

(Karande *et al.*, *Pharmaceutical Research*, *19(5)*:655-660 (**May 2002**)). Karande teaches that synergy between skin penetration enhancers is typically unpredictable (*i.e.*, "synergy" is often synonymous with unexpected or unpredictable results):

> "Applications of transdermal drug delivery are limited by low skin permeability. Many chemicals have been used to enhance skin permeability, however, only a handful are actually used in practice. Combinations of chemicals are likely to be more efficient in enhancing skin permeability compared to individual enhancers. However, identification of efficient enhancer combinations is quite challenging because many chemical enhancers interact with each other and with the skin in a complex manner. In the absence of a fundamental knowledge of such interactions, we need to rely on rapid methods to screen various enhancer combinations for their effectiveness."

Karande, Abstract; and:

> "The HTP method is particularly beneficial for testing mixtures of enhancers whose efficiency may be difficult to predict a priori. Since appropriate mixtures of enhancers are likely to be more efficient than their individual components, the HTP method may be used to discover novel enhancers comprising of enhancer mixtures. This method may also be used to explore synergies between various enhancers, which may lead to novel formulations for transdermal drug delivery as well as cosmetic agents."

Karande, page 660, col. 1, second paragraph.

Accordingly, there would be an undue burden to arrive at the invention as fully claimed based on the lack of guidance and support from the instant disclosure.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 36-38 and 44-46 are anticipated by Bodor:

Claim 36-38 and 44-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Bodor *et al.*, U.S. Patent No. 4,764,381, issued on August 16, 1988.

Claim 36 is directed towards a formulation comprising a first and second chemical penetration enhancer having a 24-hour synergy value of 2 or more.

Bodor teaches pharmaceutical preparations comprised of a pharmaceutically active ingredient and a carrier which comprises a percutaneous penetration enhancer comprised of 2-ethyl-1, 3-hexanediol alone or in combination with oleic acid is disclosed. The 2-ethyl-1,3-hexanediol may be present in an amount in the range of about 50% to 100% based on the weight of the carrier. The oleic acid may be used in combination with 2-ethyl-1, 3-hexanediol in an amount of about 1 to 40% based on the weight of the carrier to provide a synergistic effect with respect to percutaneous penetration enhancement. The compound 2-ethyl-1,3-hexanediol as used alone and/or in combination with the oleic acid has been found to significantly enhance the delivery of a drug, to a patient, from a transdermal delivery system (see Abstract).

In Table I and Table II, Bodor teaches that formulations 15, 16, and 17, have synergy values of at least 2 in comparison to formulation 13 - #13 (0.022); #15 (0.306); #16 (0.360); and #17 (0.351). This teaching also anticipates claims 37, 38 and 44-46.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 36-38 and 44-46 are obvious over Bodor and Karande:

Claims 36-38 and 44-46 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bodor *et al.*, U.S. Patent No. 4,764,381, issued on August 16, 1988, and Karande *et al.*, *Pharmaceutical Research*, *19(5)*:655-660 (**May 2002**).

Claim 36 is directed towards a formulation comprising a first and second chemical penetration enhancer having a 24-hour synergy value of 2 or more.

Bodor teaches pharmaceutical preparations comprised of a pharmaceutically active ingredient and a carrier which comprises a percutaneous penetration enhancer comprised of 2-ethyl-1, 3-hexanediol alone or in combination with oleic acid is disclosed. The 2-ethyl-1,3-hexanediol may be present in an amount in the range of about 50% to 100% based on the weight of the carrier. The oleic acid may be used in combination with 2-ethyl-1, 3-hexanediol in an amount of about 1 to 40% based on the weight of the carrier to provide a synergistic effect with respect to percutaneous penetration enhancement. The compound 2-ethyl-1,3-hexanediol as used alone and/or in combination with the oleic acid has been found to significantly enhance the delivery of a drug, to a patient, from a transdermal delivery system (see Abstract).

In Table I and Table II, Bodor teaches that formulations 15, 16, and 17, have synergy values of at least 2 in comparison to formulation 13 - #13 (0.022); #15 (0.306); #16 (0.360); and #17 (0.351). This teaching also addresses the limitations of claims 37, 38 and 44-46.

Although Bodor only reports on the flux at 10 hours of time (see Table II), he does not explicitly report on the flux at 24 hours as in the claims.

Karande teaches a method a high throughput method was developed based on skin conductivity and mannitol penetration into the skin. This method was used to perform at least 100 simultaneous tests per day. Detailed studies were performed using two model enhancers, sodium lauryl sulfate (SLS) and dodecyl pyridinium chloride (DPC). The predictions of the high throughput method were validated using Franz diffusion cells. In Figure 2, Karande demonstrates how formulations having synergistic combinations of penetration enhancers increase over time.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Bodor and Karande are directed towards pharmaceutical formulations that result in synergistic penetration enhancement of the skin. One of ordinary skill in the art would have understood that as time progressed that the formulation for

the enhancement ration would have increased. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

Conclusions

No claim is allowable.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey S. Lundgren/
Patent Examiner, Art Unit 1639